Advanced Diagnostic Approaches and Current Management of Avian Hepatic Disorders

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GROSS ANATOMY OF THE AVIAN LIVER

The normal adult avian liver is a dark red-purple color and is composed of right and left lobes, with the right lobe being larger in most species (**Fig. 1**). The lobes are enclosed in a thin capsule of connective tissue and joined along the cranial midline.[1,2] In various species, the lobes are subdivided into ventral and dorsal segments, and intermediate processes project from the ventral hilar region. The cranioventral aspects of the lobes surround the apex of the heart and the visceral surface of the liver is in contact with the proventriculus, ventriculus, and spleen. Ventrally the liver is in contact with the sternum and, in most avian species, the liver lobes do not extend beyond the caudal aspect of the sternum.[2]

Bile is drained from both lobes of the liver by the right and left hepatic ducts. The hepatic ducts fuse to form the common hepatoenteric duct, which empties in the distal end of the ascending duodenum.[3,4] When present, the gallbladder is found along the visceral surface of the right liver lobe. The size of the gallbladder can vary significantly between species, with a long gallbladder present in toucans, woodpeckers, and barbets.[1] A branch of the right hepatic duct forms the hepatocystic duct that drains bile to the gallbladder. The cystoenteric duct carries bile from the gallbladder to the duodenum.[3,4] Psittacine species, most species of pigeons, and ostriches do not have gallbladders.[1,2] In these species, the branch of the right hepatic duct forms the right hepatoenteric duct that empties directly into the duodenum.[4]

The liver receives its blood supply from the left and right hepatic arteries, which are branches of the celiac artery, and the hepatic portal veins.[2] The left and right hepatic

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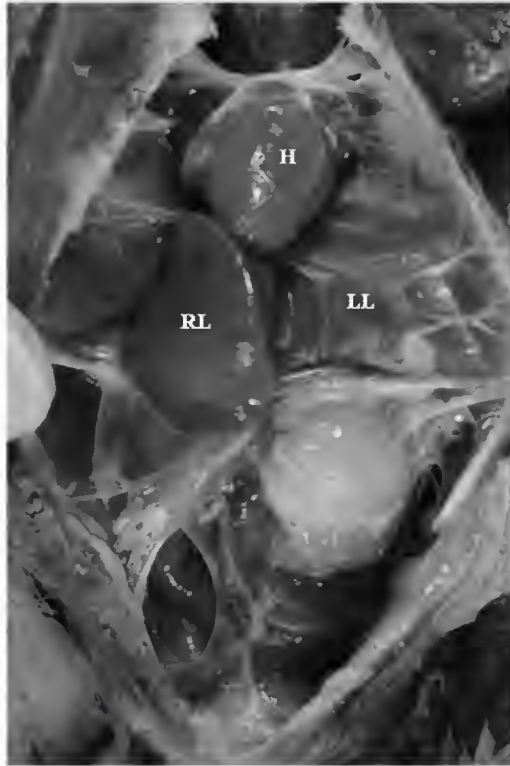*E-mail address:* vgrunkem@utk.edu

Fig. 1. Normal adult African gray parrot celomic cavity at the time of necropsy. The bird is in dorsal recumbency. A ventral midline incision has been made in the celomic cavity and the sternum has been removed to visualize the internal organs, including the heart (**H**), right liver lobe (**RL**), and left liver lobe (**LL**). (*Courtesy of* Cheryl B. Greenacre, DVM, DABVP [Avian and Small Mammal Specialties], Knoxville, TN.)

portal veins drain the proventriculus, ventriculus, large and small intestines, spleen, and pancreas.[5,6] Blood is drained from the liver by the left and right hepatic veins that join in the liver to form the caudal vena cava.[2]

FUNCTIONS OF THE LIVER

The avian liver performs numerous essential metabolic functions, which include the synthesis, storage, filtration, and excretion of various nutrients and chemicals. Bile acids, which aid in digestion through the emulsification of lipids and the activation of pancreatic enzymes, are synthesized in the liver from cholesterol.[3] Because birds produce little to no biliverdin reductase, hemoglobin is incompletely metabolized to biliverdin in the liver. Thus, unlike in mammals where bilirubin is the primary bile pigment, biliverdin is the primary bile pigment in avian species. This pigment gives the bile a characteristic green color.[4,6] Glycogen is produced by hepatic carbohydrate metabolism and stored in the liver along with iron and lipid-soluble vitamins. The liver is also the site of plasma protein, clotting factor, cholesterol, urea, and uric acid synthesis, and it functions in drug metabolism and excretion.[3,6] In addition, the macrophages in hepatic sinusoids (Kupffer cells) assist in clearing microorganisms from the portal blood.[6]

The liver has a sizeable capacity for regeneration and a large functional reserve. The destruction of hepatic tissue results in regeneration, fibrosis, and/or biliary hyperplasia. Hepatocytes are continually replaced until only one-twelfth of the cells remain undamaged.[7,8] Thus, the diagnosis of liver disease is particularly challenging because up to 80% of liver tissue must be compromised before hepatic dysfunction becomes clinically evident.[3,9]

DIAGNOSING HEPATIC DYSFUNCTION IN THE AVIAN PATIENT

The diagnosis of liver disease is made based on a constellation of supportive evidence from the clinical history, physical examination, clinical pathologic testing, imaging studies, and histopathologic examination of biopsy specimens. Although multiple tests are designed to indicate hepatocellular destruction and to measure hepatic function, these tests often give no indication as to the viability of the remaining hepatic tissue or the inciting cause of the damage.[6,7] Specific testing such as bacterial and fungal cultures, viral polymerase chain reactions, and heavy metal blood levels should be pursued to determine the inciting cause of the hepatic damage.

Patient History and Clinical Signs

Because hepatic dysfunction can result from various insults, the patient's history and clinical signs at the time of presentation are highly variable. The collection of a detailed anamnesis may provide information as to the duration, severity, and cause of the liver disease, and is essential to the complete evaluation of any avian patient. Information gathered about the patient should include, but is not limited to: signalment, history of ownership, diet, reproductive status, habitat design and maintenance, exposure to other animals including both captive and wild birds, health status of other animals in the house/aviary, current medications and supplements, potential toxin exposure, and details regarding the onset and progression of the clinical signs of the bird.[9]

Unfortunately, there are no pathognomonic clinical signs of avian liver disease. Nonspecific signs associated with liver disease in birds include anorexia, lethargy, weakness, dehydration, weight loss, obesity, regurgitation, vomiting, polydipsia, tachycardia, tachypnea, dyspnea, and sudden death.[7,9–11] Birds with hepatic dysfunction can also have a range of integumentary problems including overgrowth and flaking of the beak and nails, abnormal molting, poor feather quality with a darkening of the feather pigment, pruritus, and feather picking.[9,10] Abnormal bruising or bleeding of skin can occur in cases where hepatic failure results in a coagulopathy.[7] Icterus of the skin and sclera (hyperbilirubinemia) is rare in avian patients because of their previously described lack of bilirubin production.[11] Diarrhea, melena, and hematochezia can occur with hepatic disease, and birds that are anorexic for any reason can pass green feces due to an increase in fecal biliverdin. Hepatic dysfunction can also result in polyuria and biliverdinuria, which is a green or yellow coloration of the urine and urates.[7,12,13] Although the presence of biliverdinuria is highly suggestive of liver disease, hemolysis can also result in an increased biliverdin concentration in urates and urine.[12,14] Hepatomegaly and ascites can be associated with liver disease and can result in celomic distension and respiratory compromise (Fig. 2).[7,11] Neurologic signs such as tremors, seizures, and paresis can occur in cases with an encephalopathy secondary to hepatic disease.[9,11]

Clinical Pathologic Analysis

Complete blood counts (CBCs), biochemistry profiles, protein electrophoresis, bile acid levels, and plasma dye clearance tests can all provide evidence to support
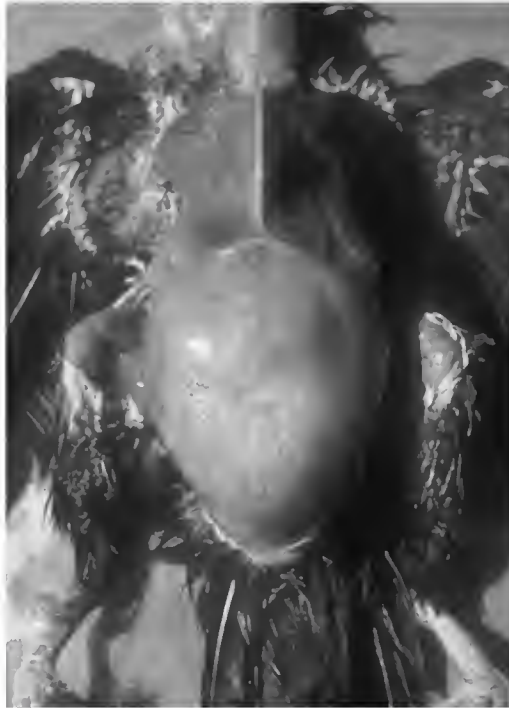
Fig. 2. Celomic distension due to hepatomegaly in a deceased myna bird (*Acridotheres* spp). The bird is in dorsal recumbency with the cranial aspect of the patient toward the top of the image, and the skin has been removed from the bird's ventrum. (*Courtesy of* Edward C. Ramsay, DVM, DACZM, Knoxville, TN.)

a diagnosis of liver pathology and its secondary complications. However, it is important to understand the sensitivity and specificity of these results when evaluating a patient and designing an appropriate treatment plan.

CBC abnormalities in avian patients with liver disease are nonspecific, but they may give an indication as to the chronicity and underlying pathologic condition of the disease process. Anemia can occur in these cases as a result of coagulopathies, hepatic trauma, hemochromatosis, and bone marrow suppression caused by hepatic infection, inflammation, or neoplasia. A leukocytosis may be present with infectious or inflammatory liver disease, especially when it is caused by *Chlamydophila*, *Mycobacterium*, or *Aspergillus*.[15] Examination of blood or buffy coat smears may reveal parasites that can cause hepatic damage such as *Atoxoplasma* spp, *Leukocytozoon* spp, and *Plasmodium* spp.[16]

The results of a biochemistry profile may indicate a loss of the liver's synthetic capabilities, hepatocellular damage, and systemic changes secondary to hepatic disease. As discussed earlier, the liver is responsible for synthesizing plasma proteins, cholesterol, and urea, and has a major role in carbohydrate metabolism. Thus hypocholesterolemia, hypouricemia, hypoglycemia, and hypoproteinemia can all occur with hepatic failure.[17] Hypercholesterolemia can occur in cases of hepatic lipidosis and bile duct obstruction.[18] Although a decrease in total protein levels due to a decrease in plasma albumin can develop as a result of liver disease, this abnormality can result from a multitude of other factors. These factors include overhydration, decreased

availability and absorption of protein from the diet, and loss of protein from the gastro-intestinal tract or kidneys. By contrast, patients with infectious or inflammatory hepa-titis may have a hyperproteinemia characterized primarily by a hyperglobulinemia caused by stimulation of the immune system.[19] Protein abnormalities can be further investigated with electrophoresis to determine the relative changes in each protein fraction. Although normal electrophoretic reference ranges have not been determined for all avian patients, characteristic changes in the electrophoretogram may assist in the diagnosis and monitoring of diseases such as chronic active hepatitis.[9,20]

Increases in plasma enzyme activities can indicate the presence of hepatocellular damage and enzyme leakage. Enzyme activity profiles can vary significantly depend-ing on the severity of disease, the species being tested, and concurrent damage to other organ systems. It is best to analyze enzyme activities for patterns of elevation among a profile of enzymes and in repeated blood samples over time to avoid over-interpreting a single enzyme value. Furthermore, normal enzyme activities should not be interpreted as equating to normal hepatic function, but rather as indicating the lack of current detectable hepatocellular damage.[21]

Aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatinine kinase (CK), and alanine aminotransferase (ALT) have been analyzed in various avian species with hepatic damage. AST is a sensitive indicator of hepatic disease. However, because AST is present in liver tissue and all muscle types, an elevation in AST activity usually indicates either liver or muscle damage.[17,21] LDH is not specific or sensitive for liver damage because it is present in various tissues including liver, muscle, kidney, bone, and erythrocytes.[19] However, LDH has a very short plasma half-life with eleva-tions in this enzyme indicating recent tissue damage.[21] Increases in AST and LDH activity should be interpreted in conjunction with CK, which is a muscle-specific enzyme. When there is a concurrent elevation in CK activity, increases in AST and LDH are more likely caused by muscle damage. However, because AST has a longer plasma half-life than CK and LDH; an elevation in AST but not CK or LDH can indicate muscle or liver damage.[9,21] Decreases in AST and LDH activities can indicate a severe loss of hepatocellular mass.[21] Interpretation of ALT activity has limited diagnostic value in birds because this enzyme is present in almost all tissues, and ALT activity in some healthy avian patients is less than the sensitivity of many analyzers.[19] Hemo-lysis of the blood sample can result in a significant increase in LDH with lesser effects on AST, ALT, and CK.[21]

Gamma-glutamyltransferase (GGT) and glutamyl dehydrogenase (GLDH) are specific indicators of avian liver disease.[21] Increases in plasma GGT activity occur with biliary damage or obstruction, and marked elevations in this enzyme have been noted in cases of avian bile duct carcinoma.[17] GLDH is present within the mitochon-dria of numerous tissues including the liver. Elevations in GLDH have been associated with severe hepatic damage with cellular necrosis, such as occurs with Pacheco disease.[10] Neither of these enzymes is a sensitive indicator of avian liver disease, and normal reference intervals are available for only a few avian species.[19,21]

Hepatic, renal, intestine, and bone isoenzymes of alkaline phosphatase (ALP) have been identified in avian species. However, unlike in mammals where elevations in ALP activity are frequently associated with biliary disease, only very low ALP levels have been identified in the avian liver, and significant elevations in this enzyme have not been associated with hepatic disease.[17]

As discussed earlier, bile acids and bile salts are produced by the liver and secreted into the duodenum through the biliary ducts. Through enterohepatic circulation, more than 90% of the bile acids are reabsorbed in the distal small intestine and extracted from the portal blood by hepatocytes. If the liver is damaged, bile acids are not

appropriately extracted, conjugated, and secreted.[21] Thus, the measurement of the bile acid concentration in plasma provides a sensitive and specific indication of hepatic function.[10] In a study where protein electrophoresis, bile acid levels, and enzyme levels including AST, CK, LDH, and GGT were analyzed in 442 psittacine plasma samples, elevated bile acid levels had the highest correlation with histologically confirmed hepatic disease. Nevertheless, bile acid levels were low or normal in 26% of the cases of confirmed hepatic disease and elevated in 18% of the nonhepatic cases in this study.[22]

Assays to measure bile acid concentrations are available in most veterinary laboratories. The clinician should be aware that both radioimmunoassay (RIA) and enzymatic assays are used to determine bile acid concentrations. Because the enzymatic assay measures a wider spectrum of bile acids, the reference values for that test tend to be higher than those for the RIA.[19,21] Unlike the enzymatic assay, the results of RIA performed on avian plasma samples in one study were not affected by lipemia, hemolysis, or elevated LDH concentrations.[23] Ideally, assay-specific and species-specific reference intervals provided by the laboratory where the test was performed should be used for interpretation. Although significant postprandial elevations in bile acids have been noted in pigeons, mallards, and peregrine falcons, other studies investigating fasting and postprandial elevations in avian bile acids have produced inconsistent results.[23–26] Because elevations with hepatobiliary disease are typically much greater than postprandial elevations, many investigators recommend only a single nonfasted sample in birds.[10,21]

Measurement of the clearance of exogenous dyes or sugars injected intravenously can also be used to assess hepatic function. The use of clearance tests involving indocyanine green, sulfobromophthalein, and galactose has been reported in avian species.[9] Studies performed in galahs (*Eolophus roseicapilla*) found that galactose clearance may be a more sensitive indicator of hepatic function than plasma bile acid assays.[27] However, the availability and clinical application of these tests are currently limited, and further research is necessary to assess the value of clearance tests in the diagnosis of avian hepatic disease.[9,17]

Imaging

Radiography and ultrasonography are commonly used to evaluate avian patients with suspected hepatic disease. Additional imaging studies including contrast radiography, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine scans may be used in select cases to provide further diagnostic and prognostic information.

Appropriately positioned, whole body radiographs can be used to assess hepatic size. On a ventrodorsal radiograph, the normal liver silhouettes with the heart to form an "hourglass" shape and it does not extend laterally beyond a line drawn from the scapula to the acetabulum. The normal liver does not extend beyond the caudal aspect of the sternum on a lateral radiograph.[10] Apparent microhepatica of unknown clinical significance is frequently observed on radiographs of macaws and cockatoos.[11] Hepatomegaly may result in widening of the cardiohepatic waist, compression of the abdominal air sacs, rounding of the liver margins, extension of the liver beyond the previously noted margins, cranial displacement of the heart, dorsal displacement of the proventriculus, and caudodorsal displacement of the ventriculus (**Fig. 3**).[28] Summation of an enlarged proventriculus with the liver can cause an apparent enlargement of the hepatic silhouette, and can be differentiated from true hepatomegaly using gastrointestinal contrast radiography or fluoroscopy.[11,28] Other pathologies including cardiomegaly, splenomegaly, air sac disease,

Fig. 3. (*A*) Ventrodorsal radiograph of a normal adult cockatiel. (*B*) Ventrodorsal radiograph of an obese adult cockatiel with a history of elevated bile acids, AST, ALT, and hyperuricemia. This radiograph shows a widening of the hepatic silhouette and a loss of the cardiohepatic waist.

and ascites can result in a widening of the cardiohepatic waist and can be further investigated with ultrasonography or other advanced imaging modalities.

Ultrasonography of the avian celomic cavity can be challenging because of the small size of the patient and interference from the air sacs. However, in the patient with hepatic disease, image clarity may be increased by the presence of ascites and the compression of air sacs by organomegaly.[29,30] A fast of 2 to 3 hours before ultrasonography should be adequate to empty the gastrointestinal tract in most avian species. However, some investigators have suggested up to a 2-day fast in carnivorous species to facilitate visualization of the gallbladder.[31] General anesthesia is rarely necessary for ultrasonography, and positioning the patient in dorsal recumbency with cranial aspect of the body elevated at a 30° angle may facilitate the visualization of celomic structures.[29] In cases of avian hepatobiliary disease, ultrasonographic evaluation may detect ascites, changes in the size and normal homogenous echogenicity of the liver, congestion of the hepatic vasculature, and rare pathologic changes in the gallbladder.[31] Centesis of celomic fluid, fine-needle aspiration of liver parenchyma, and hepatic biopsy can all be performed with ultrasonographic guidance. The details of how to obtain these samples are beyond the scope of this article, but these techniques have been described in greater detail by other investigators.[31–33]

The application of CT and MRI in cases of avian hepatic disease has been infrequently reported (**Fig. 4**). However, the high-resolution images acquired with these

Fig. 4. Sagittal CT image of a Moluccan cockatoo (*Cacatua moluccensis*) with no known liver pathology. The cranial aspect of the patient is toward the top of the image. The heart (H), liver (L), and ventriculus (V) are all noted.

modalities are particularly useful in the precise anatomic localization of masses identified with radiography. In addition, the information provided by these imaging modalities can be useful in staging neoplastic processes and in planning accurate surgical intervention.[29] Drawbacks of CT and MRI include the need to place a potentially compromised patient under general anesthesia to acquire diagnostic images, the increased costs associated with these scans, and the need for a referral to a specialty hospital in most cases.

The use of nuclear medicine technologies has also been rarely reported in cases of avian hepatic disease. Nuclear medicine scans, which include hepatobiliary scintigraphy and positron emission tomography (PET), detect and map the distribution of radiopharmaceuticals that have been administered to a patient in order to diagnose and monitor disease processes. Hepatobiliary scintigraphy is used in mammalian patients to evaluate hepatic function and morphology, and the patency of the biliary tract. In avian medicine, quantitative hepatobiliary scintigraphy using the radiopharmaceutical ^{99m}Tc-mebrofenin has been used to evaluate hepatic function in pigeons before and after exposure to ethylene glycol. A correlation between histologic damage in the liver and scintigraphic measures of hepatic function has been found. However, further research is necessary to determine the clinical applications of this imaging modality in diagnosing and monitoring clinical patients with hepatic disease.[34] PET

scans are routinely obtained in human oncology patients for diagnosis and therapeutic monitoring. ^{18}F-Fluorodeoxyglucose (FDG), a glucose analogue labeled with a positron-emitting radionuclide, is the most common radiopharmaceutical used for these scans. FDG-PET scans map the accumulation of FDG within cells with active glucose metabolism such as those of the brain, liver, inflammatory lesions, and neoplastic tissue.[35,36] The FDG-PET scans of 16 healthy Hispaniolan Amazon parrots (*Amazona ventralis*) showed increased radioactivity in the heart, brain, eyes, kidneys, segments of the gastrointestinal system, and some skeletal muscle (**Fig. 5**) (Marcy Souza, DVM, MPH, DABVP (Avian), personal communication, January 2010).[37] Fusion PET/CT scanners are also available, and the integration of these scans allows for the precise anatomic localization of lesions with increased uptake of the radionuclide.[35] To the author's knowledge, neither PET nor PET/CT imaging have been used in the evaluation of avian patients with proven hepatic disease. However, these imaging modalities may have an application in the diagnosis and posttherapeutic monitoring of primary and metastatic hepatic neoplasia in avian species. The drawbacks of nuclear medicine scans are similar to those of CT and MRI, with the additional negative aspect of exposure of the patient and the clinical staff to even higher doses of radiation.

Hepatic Biopsy

Biopsy of the liver is often required to definitively diagnose and appropriately characterize hepatic disease. The diagnostic and prognostic value of a hepatic biopsy is dependent on many factors, including the stage and cause of disease, method of biopsy collection, and tissue handling.[9,38] A hepatic biopsy specimen can be obtained by blind percutaneous techniques, with ultrasonographic guidance, with endoscopic visualization, or surgically. Because there are risks associated with each of these biopsy techniques, the clinician should have a high index of suspicion for the presence of hepatic disease before performing a biopsy. Risks of obtaining a hepatic biopsy

Fig. 5. A 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) positron emission tomography scan of a healthy Hispaniolan Amazon parrot (*Amazona ventralis*). The cranial aspect of the patient is toward the top of the image. Increased radioactivity in the heart (H) and intestines (I) is evident, with subjectively less FDG uptake apparent in the liver (L). (*Courtesy of* Marcy J Souza, MPH, DVM, DABVP [Avian Specialty], Knoxville, TN.)

include severe hemorrhage, perforation of other internal organs, asphyxiation secondary to leakage of ascitic fluid into iatrogenically ruptured air sacs, and the associated risks of general anesthesia in a potentially compromised patient.[9] Because coagulopathies can develop secondary clotting factor deficiencies in cases with hepatic dysfunction, the patient's clotting potential should be assessed before obtaining a biopsy specimen. Thrombocytopenia and prolongation of the cutaneous bleeding time, whole blood clotting time, or prothrombin time may indicate decreased coagulation function in the avian patient. However, accurate interpretation of these tests may be complicated by the lack of normal reference values for most avian species.[39] To help prevent aspiration of ascitic fluid, the fluid can be aspirated prior to the anesthetic event and the patient can be positioned in an upright position while under anesthesia.[9]

Endoscopic examination allows for minimally invasive visualization of intracelomic structures and targeted sampling of identified lesions. As with ultrasonography, a preanesthetic fast of at least 3 hours can aid in visualization of organs during the procedure. However, the most common impediment to organ visualization is intracelomic fat in obese patients.[38] A ventral midline approach just caudal to the sternum allows for direct access into the ventral hepatoperitoneal cavities. With this approach, the liver lobes can be visualized and sampled. A lateral approach through either the left or right caudal thoracic air sac can also be used to access the liver. However, because a connection between the caudal thoracic air sacs and the ventral hepatoperitoneal cavities will be made via this approach, it is contraindicated in patients with ascites.[38,40] The reader is referred to other resources for descriptions of the necessary endoscopic instrumentation, specific biopsy techniques, and ideal tissue handling.[38,40,41]

Surgical approaches for hepatic biopsy can include a small keyhole incision or a longer celiotomy incision. For a keyhole hepatic biopsy, a skin incision is made on the ventral midline just caudal to the sternum and the caudal margin of the liver is visualized and biopsied through this incision. A celiotomy allows for greater visualization of the liver, more precision in sampling lesions, and resection of larger pieces of tissue. In addition, this approach may allow for more immediate and aggressive intervention in the event of complications.[9]

Hepatic samples obtained by any of these biopsy techniques may be prepared and submitted for bacterial and fungal culture, cytologic evaluation, and histopathologic examination. Unfortunately, diagnosis of the specific cause and evaluation of the severity of hepatic disease may not be determined until a necropsy is performed. In aviary situations where an infectious or toxic cause of hepatic disease is suspected, it is often beneficial for the flock health to sacrifice a bird for postmortem examination and diagnostic sampling. The reader is referred to additional resources for pathologic descriptions of avian hepatic disorders.[2,42]

MEDICAL MANAGEMENT OF HEPATIC DYSFUNCTION IN THE AVIAN PATIENT

Because avian hepatic disease can result from a multitude of causes and the patient can experience various secondary complications, treatment plans are varied. If the cause of the hepatic dysfunction has been identified, therapies should be directed at treating the diagnosed disease. Discussion of the targeted therapeutic plans for hepatic disorders such as infectious hepatitis, hemochromatosis, hepatic lipidosis, heavy metal toxicosis, and hepatic neoplasia is outside the scope of this article. The reader is referred to additional resources wherein the specific treatments for these diseases are detailed.[11,43,44] Therapies can also be directed at remediating secondary

complications of hepatic dysfunction and supporting the remaining cellular function and regeneration.

Secondary complications of hepatic disease can include weakness, respiratory distress, dehydration, anorexia, emaciation, encephalopathy, anemia, or ascites. General supportive care includes providing a quiet, warm environment with oxygen therapy for patients with respiratory compromise. Formulation of an appropriate fluid therapy plan should take into consideration the patient's hydration status, general organ function including noted cardiac and renal disease, and ongoing fluid losses. Fluids should be warmed and dextrose can be added to isotonic crystalloid fluids for hypoglycemic patients.[43]

Nutritional recommendations to support birds with hepatic disease vary because patients can range in body condition from obese to emaciated, and they can have a normal appetite or be anorexic. Diets that contain only 8% protein with low levels of aromatic amino acids and higher levels of branched chain amino acids have been recommended to reduce the hepatic workload in patients with liver disease.[45] However, some investigators have countered that dietary protein should not be restricted in patients with hepatic dysfunction that are not showing signs of encephalopathy.[6] The diet offered to avian patients with hepatic dysfunction should have easily metabolized energy sources such as carbohydrates and fats, and be high in soluble fiber. Vitamin supplementation, such as the use of the antioxidant vitamin E in cases of inflammatory hepatitis, may be of benefit.[7] A patient's dietary requirements can vary significantly with the specific cause of the hepatic disease, especially in cases of hemochromatosis and hepatic lipidosis. In addition, gavage feeding of liquefied diets may be necessary in anorexic patients.

Hepatic encephalopathy, an alteration in brain function secondary to the accumulation of unfiltered metabolic products, is a poorly documented syndrome in avian species. In mammalian species, hepatic encephalopathy typically occurs in cases of portosystemic shunting or liver failure, and is positively correlated with increased blood ammonia levels.[10,21] Lactulose, a synthetic disaccharide derivative of lactose that is minimally digested and absorbed by the mammalian gastrointestinal system, is commonly prescribed in cases of hepatic encephalopathy. Lactulose helps to lower blood ammonia levels through acidification of colonic contents, stimulation of an osmotic diarrhea, and increasing nitrogen fixation by bacteria in the gastrointestinal tract.[46,47] A positive correlation between elevated blood ammonia levels and encephalopathy has not been identified in avian patients.[10,21] In addition, it is unknown whether lactulose is digested, absorbed, and results in acidification in the avian gastrointestinal tract as it does in mammals. Nevertheless, lactulose is frequently prescribed in birds with hepatic dysfunction with anecdotal evidence of clinical improvement. Few adverse effects have been associated with its administration.[47,48]

Patients with hepatic disease can develop anemia through several pathophysiologic mechanisms including gastroduodenal ulcerations and coagulopathies. Gastrointestinal ulcerations can be treated with various protectants including sucralfate and H_2 receptor antagonists, such as cimetidine.[7,48] Coagulopathies have been previously discussed and can be treated with vitamin K supplementation. In addition, avian patients with anemia secondary to hepatic disease may benefit from vitamin B supplementation, iron dextran administration, and even whole blood transfusions depending on the severity of the anemia. Iron supplementation should not be administered in patients suspected of having hemochromatosis.[43]

If ascitic fluid is present, it can be aspirated from the celomic cavity with or without ultrasonographic guidance. The needle should be inserted on midline through the body wall and directed toward the right side of the celomic cavity to avoid the

ventriculus.[49] The sample can be submitted for cytologic analysis, which should include evaluation of the color, character, specific gravity, total solid concentration, and cellularity of the aspirated fluid. A cytologic preparation of the fluid should be microscopically evaluated and, if a bacterial cause is suspected, the fluid should be cultured.[11,50] If an effusion develops with severe hepatic dysfunction, it is typically a transudate that results from the decrease in oncotic pressure that occurs with hypoalbuminemia. Transudate effusions are usually clear with a low specific gravity, total protein concentration, and cellularity.[50] Because the removal of a large volume of ascitic fluid can result in severe protein loss, the volume of fluid aspirated from the celomic cavity should be restricted to only that required to relieve respiratory compromise.[7,43] Diuretic therapy may be instituted to help promote fluid excretion in patients with ascites.[43]

The use of nutraceuticals, such as milk thistle and S-adenosylmethionine (SAMe), as adjunctive treatments of hepatic dysfunction in veterinary patients is becoming increasingly commonplace. The medicinal extract from the milk thistle plant (*Silybum marinum*) is silymarin, and the active component of silymarin is silybin. Silymarin is thought to assist in the treatment of liver disease through its antioxidant properties, stabilization of cell membranes, regulation of cell permeability, and promotion of DNA, RNA, and protein synthesis.[46,51,52] Although it is often prescribed to avian patients with hepatic diseases, with anecdotal evidence of clinical improvement, only a small number of studies have investigated the efficacy of this compound in ameliorating avian liver dysfunction. Two avian studies, one using pigeons and the other using broiler chicks, have investigated the hepatoprotective effects of silymarin in experimentally induced cases of aflatoxicosis. Although the conclusions of these studies were conflicting in their assessment of silymarin efficacy, this may have been the result of differences in the silymarin and aflatoxin doses.[51,52] Side effects of silymarin administration are rarely reported, but can include nausea and diarrhea.[46] SAMe, a glutathione precursor that is normally produced by the liver, is most commonly prescribed in mammalian patients as a supplemental treatment for hepatic diseases including chronic hepatitis, hepatic lipidosis, and acute hepatotoxicosis.[7,46] To the author's knowledge, no research has been published on the efficacy of SAMe as an adjunctive treatment of avian hepatic diseases. Anecdotal evidence exists that supports the use of therapeutics to promote choleresis, such as ursodiol (ursodeoxycholic acid) and dandelion, in cases of avian liver disease with cholestasis.[6,7,53] However, as with SAMe, no controlled studies have been performed to demonstrate the efficacy and safety of these compounds in avian patients. In addition, because many of the previously mentioned therapeutics are not available in formulations that have been approved by the Food and Drug Administration, clinicians must be aware that the potency, purity, and safety of available formulations may vary significantly among manufacturers.[46,54]

SUMMARY

The diagnosis of avian hepatic disease should be made based on the results of multiple diagnostic tests including physical examination, clinicopathologic testing, imaging studies, and hepatic biopsy. An understanding of the anatomy and function of the avian liver is essential for the proper interpretation of diagnostic findings related to hepatic disease. The diagnostic plan should be designed to investigate the severity and underlying cause of the hepatic disease so that a treatment plan that includes both targeted and supportive therapies can be implemented. Patients should be monitored for their response to treatment by periodically repeating the tests that were used to diagnose

the hepatic disease. The intervals at which these tests are repeated will depend on many factors including the specific cause of the disease, the treatments being used, the invasiveness of the tests, and the owner's commitment to pursuing these tests.

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